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(54) **Imidazolidinedione derivatives.**

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CHEMICAL ABSTRACTS, vol. 83, no. 23, 08 Dec 1975, Columbus, OH (US); H.OTOMASU et al.: "Spiro heterocyclic compounds. I. Synthesis of spiroimidazolidine-4,3'-indoliner-2,2',5-triones", p. 453, no. 193175f

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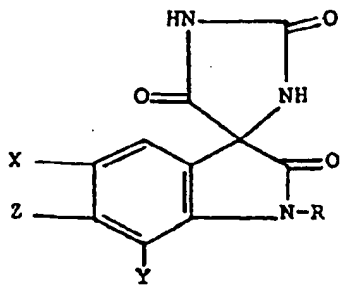
Descripti n

This invention relates to new imidazolidinedione derivatives of interest to those in the field of medicinal chemistry and chemotherapy. More particularly, it is concerned with a novel series of *spiro*-oxindole imidazolidinedione compounds for the control of certain chronic complications arising from diabetes mellitus (e.g., diabetic cataracts, retinopathy and neuropathy).

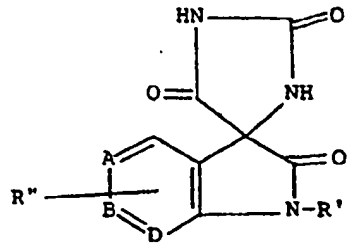
Past attempts to obtain new and better oral antidiabetic agents have, for the most part, involved an endeavour to lower blood sugar levels. However, little is known about the effect of organic compounds in preventing or arresting certain chronic complications of diabetes, such as diabetic cataracts, neuropathy and retinopathy, etc. Nevertheless, K. Sestanj et al. in U.S. Patent No. 3,821,383 do disclose that certain aldose inhibitors like 1,3-dioxo-1H-benz[d,e]isoquinoline-2(3H)-acetic acid and some closely-related derivatives thereof are useful for these purposes even though they are not known to be hypoglycemic. EP—A—0028906 and EP—A—0066378 disclose certain 1'-substituted-spiro-(imidazolidine-4,3'-indoline)-2,2'5)-triones as inhibitors of the enzyme aldose reductase. These compounds function by inhibiting the activity of the enzyme aldose reductase, which is primarily responsible for catalyzing the reduction of aldoses (like glucose and galactose) to the corresponding polyols (such as sorbitol and galactitol) in the human body. In this way, unwanted accumulations of glactitol in the lens of galactosemic subjects and of sorbitol in the lens, retina, peripheral nervous system and kidney of diabetic subjects are prevented or reduced. As a result, these compounds control certain chronic diabetic complications, including those of an ocular nature, since it is already known in the art that the presence of polyols in the lens of the eye leads to cataract formation and concomitant loss of lens clarity.

The present invention relates to novel *spiro*-oxindole imidazolidinedione compounds useful in therapy as aldose reductase inhibitors for the control of certain chronic complications arising in a diabetic subject. More specifically, the novel compounds of this invention are selected from the group consisting of *spiro*-hydantoin derivatives of the formulae:



(I)

and



(II)

and the pharmaceutically acceptable salts thereof, wherein X and Y ar each hydrogen, fluorine, chlorine, bromine, nitro or amino; Z is hydrogen or amino, with the proviso that Z is always other than amino when at least one of X and Y is other than hydrogen; R is a member selected from the group consisting of hydrogen, aryl and aralkyl having up to three carbon atoms in the alkyl moiety wherein each of said aryl moieties is chosen from the group consisting of pyridyl and ring-substituted pyridyl, with each ring substituent being chosen from the group consisting of fluorine, chlorine, bromine and alkyl having from one to four carbon atoms, with the proviso that said R is always other than hydrogen when each X, Y and Z is other than amino; =A—B=D— of formula II represents =N—CH=CH—, =CH—CH=N— or =CH—N=CH—; R' is a member selected from the group consisting of hydrogen, alkyl having from one to four carbon atoms, aryl and aralkyl having up to three carbon atoms in the alkyl moiety wherein each of said aryl moieties is chosen from the group consisting of pyridyl, thienyl, phenyl and mono and di-substituted phenyl, with each ring substituent being chosen from the group consisting of fluorine, chlorine, bromide, alkyl and alkoxy each having up to four carbon atoms and trifluoromethyl; and R'' is hydrogen, hydroxy, fluorine, chlorine, alkyl or alkoxy each having up to four carbon atoms or trifluoromethyl. These novel compounds are aldose reductose inhibitors and therefore, possess the ability to reduce or inhibit sorbitol accumulation in the lens and peripheral nerves of diabetic subjects.

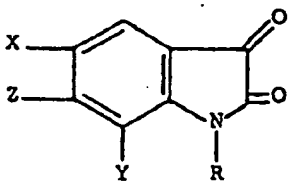
One group of compounds of interest of the present invention is that of formula I wherein X is fluorine, Y and Z are each hydrogen and R is pyridylalkyl having up to three carbon atoms in the alkyl moiety. Another group of compounds of interest of the present invention is that of formula I wherein X and Y are each chlorine, Z is hydrogen and R is pyridylalkyl having up to three carbon atoms in the alkyl moiety.

A further group of compounds of interest of the present invention is that of formula II wherein =A—B=D— is =CH—N=CH— and R'' is hydrogen or alkyl having up to four carbon atoms (e.g., methyl). Preferably, R' is hydrogen, alkyl having from one to four carbon atoms (e.g., isopropyl), mono-substituted phenylalkyl having up to three carbon atoms in the alkyl moiety (e.g., *p*-fluorobenzyl or *p*-chlorobenzyl), di-

substituted phenylalkyl having up to three carbon atoms in the alkyl molety (e.g., 3,4-dichlorobenzyl) r mon-substituted phenyl (e.g., *p*-fluorophenyl).

Of special interest in this connection are such typical and preferred member compounds of the invention as 6'-amino-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione, 5'-chloro-7'-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione, 1'-(3-pyridylmethyl-5'-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione, 1'-(3-pyridylmethyl)-5'-7'-dichloro-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione, respectively. These particular compounds are highly potent as regards their aldose reductose inhibitory activity.

In accordance with the process employed for preparing the novel compounds of this invention (viz., those of structural formulae I—II), an appropriately substituted carbonyl ring compound of structural formulae III or IV as respectively set forth below:



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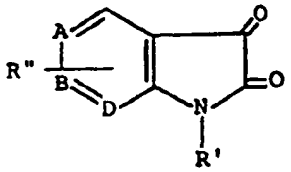


(III) (IV),

wherein X, Y, Z, R, R' and R'' are each as previously defined (with proviso), is condensed with an alkali metal cyanide (e.g. sodium cyanide or potassium cyanide) and ammonium carbonate to form the desired *spiro*-oxindole imidazolidinedione final product of the structural formulae previously indicated. This particular reaction is normally carried out in the presence of a reaction-inert polar organic solvent medium in which both the reactants and reagents are mutually miscible. Preferred organic solvents for use in this connection include cyclic ethers such as dioxane and tetrahydrofuran, lower alkylene glycols like ethylene glycol and trimethylene glycol, water-miscible lower alkanols such as methanol, ethanol and isopropanol, as well as N,N-di(lower alkyl) lower alkanoamides like N,N-dimethyl-formamide, N,N-diethylformamide and N,N-dimethylacetamide, etc. In general, the reaction is conducted at a temperature that is in the range of from about 50°C. up to about 150°C. for a period of about two hours to about four days. Although the amount of reactant and reagents employed in the reaction can vary to some extent, it is preferable to employ at least a slight molar excess of the alkali metal cyanide reagent with respect to the carbonyl ring compound starting material in order to effect maximum yield. In this way, for example, 1-(3-pyridylmethyl)-5-fluoroindoline-2,3-dione is converted to 1'-(3-pyridylmethyl)-5'-fluoro-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione, and 1-(3-pyridylmethyl) 5,7-dichloroindoline-2,3-dione is converted to 1'-(3-pyridylmethyl)-5',7'-dichloro-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione.

Compounds of the invention of formula I where X and Y are each hydrogen and Z is amino are best prepared by the alkylation of sodio-ethyl hydantoin-5-carboxylate with 2,4-dinitrochlorobenzene, followed by reductive cyclization in a conventional manner. This last step is usually accomplished by using iron powder in the presence of an acid such as hydrochloric acid or glacial acetic acid, generally in the presence of an aqueous alkanol medium at ambient to slightly elevated temperatures (e.g., *ca.*, 20—100°C.). Compounds of the invention of formula II wherein R' is hydrogen and R'' is as previously defined are also best prepared in this manner by merely substituting the appropriate halonitro-disubstituted pyridine compound in place of 2,4-dinitrochlorobenzene in the first step of the reaction. In this way, the use of 3-nitro-4-chloropyridine ultimately leads to *spiro*-[imidazoidine-4,3'-(6-azaindoline)]-2,2',5-trione as the desired final product. Moreover, compounds of the invention of formula I where X and Y are both halogen (as previously defined) and Z is hydrogen may alternatively (and preferably) be prepared from the corresponding unsubstituted compounds wherein at least one of X and Y is hydrogen by means of direct halogenation techniques well known to those skilled in the field of synthetic organic chemistry. Additionally, these same monohalo starting materials (e.g., where X is halogen and Y and Z are both hydrogen) can be converted to the corresponding compounds where Y is nitro and amino, etc., by conventional procedure well-known to those skilled in the art (e.g., nitration and subsequent reduction, etc.). In the latter connection, the reduction step is preferably accomplished by using catalytic hydrogenation, e.g., by using a platinum, palladium or nickel catalyst and gaseous hydrogen, or by using sodium amalgam and the like. Lastly, compounds of the invention of formula II wherein R' is other than hydrogen can alternatively (and preferably) be prepared from the corresponding compounds where R' is hydrogen by the use of standard techniques well-known to those skilled in the art. For instance, the use of an appropriate reagent of the formula R''' X'', where R''' is other than hydrogen or aryl and X'' is a leaving group such as an aryl or alkylsulfonyloxy radical, in the presence of a base such as sodium hydride or sodium hydroxide ultimately leads to the formulation of compounds of formula II where R' is alkyl or aralkyl as previously defined.

The ketone starting materials (i.e., carbonyl ring compounds of structural formulae III—IV) required for

preparing the desired final products of structural formulae I—II in the overall process of this invention are, for the most part, known compounds and are either readily available commercially, like isatin (2,3-indolinedione), 5-fluoroisatin, 5-chloroisatin and 5,7-dichloroisatin, etc., or else they can easily be synthesized by those skilled in the art starting from common chemical reagents and using conventional methods of organic synthesis. For instance, the 1-aralkyl-5-haloisatins are easily obtained by alkylating 5-fluoro or 5-chloroisatin with the appropriate aralkyl halide of choice (e.g., 3-chloromethylpyridine) in the presence of a base such as sodium hydride or potassium carbonate, while the corresponding 1-aryl-5-haloisatins are best synthesized by treatment of the appropriate diarylamine compound with oxalyl chloride, followed by ring-closure with aluminum chloride in the usual manner. In either case, the ultimate starting materials are both readily derived from readily available compounds.

Inasmuch as the *spiro*-oxindole imidazolidinedione compounds of this invention all possess one asymmetric center, they may exist in separated *d*- and *l*-optically active forms, as well as in racemic or *dl*-mixtures. The present invention includes all these forms. For instance, an optically active isomer may be obtained by simply resolving the racemic mixture *via* the use of standard techniques well-known to those skilled in the art, e.g., by fractional crystallization of the *spiro*-oxindole imidazolinedione salt derived from an optically active acid or base. Alternatively, the optically active isomers may be prepared by using the appropriate enantiomers as starting materials in the foregoing series of reactions.

The pharmaceutically acceptable acid addition salts of the *spiro*-oxindole imidazolidinedione base compounds of this invention are prepared by simply treating the aforementioned organic bases with various mineral and organic acids which form non-toxic acid addition salts having pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, maleate, fumarate, citrate or acid citrate, tartrate or bitartrate, succinate, gluconate, saccharate, methanesulfonate, ethanesulfonate, benzenesulfonate and p-toluenesulfonate salts. For instance, the salt-formation step may be carried out by using a substantially equimolar amount of the appropriate acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the solid salt is readily obtained.

The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic *spiro*-oxindole imidazolidinedione compounds. These particular non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by simply treating the aforementioned *spiro*-oxindole imidazolidinedione acidic compounds with an aqueous solution of the desired pharmacologically acceptable cation, and then evaporating the resulting solution to dryness while preferably being placed under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum production of yields of the desired final product.

As previously indicated, the *spiro*-oxindole imidazolidinedione compounds of this invention are readily adapted to therapeutic use as aldose reductase inhibitors for the control of chronic diabetic complications, in view of their ability to reduce lens sorbitol levels in diabetic subjects to a statistically significant degree. For instance, 1'-(3-pyridylmethyl)-5',7'-dichloro-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione, a typical and preferred agent of the present invention, has been found to inhibit the formation of sorbitol levels in diabetic rats to a significantly high degree when given by the oral route of administration at dose levels ranging from 0.5 mg./kg. to 20 mg./kg. Furthermore, the herein described compounds of this invention can be administered by either the oral or parenteral routes of administration. In general, these compounds are ordinarily administered in dosages ranging from about 0.10 mg. to about 10 mg. per kg. of body weight per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen.

In connection with the use of the *spiro*-oxindole imidazolidinedione compounds of this invention for the treatment of diabetic subjects, it is to be noted that these compounds may be administered either alone or in combination with pharmaceutically acceptable carriers by either of the routes previously indicated, and that such administration can be carried out in either single or multiple doses. More particularly, the compounds of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically-acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents. In general, the compounds of the invention will be present in such dosage forms at concentration levels ranging from about 0.5% to about 90% by weight of the total composition to provide the desired unit dosage.

For purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch and preferably potato or tapioca starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules;

preferred materials in this connection would also include the high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes, and if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For purposes of parenteral administration, solutions of these *spiro*-oxindole imidazolidinediones in sesame or peanut oil or in aqueous propylene glycol or N,N-dimethylformamide may be employed, as well as sterile aqueous solutions of the corresponding water-soluble, non-toxic mineral and organic acid addition salts or alkali or alkaline-earth metal salts previously enumerated. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art. Additionally, it is also possible to administer aforesaid *spiro*-oxindole imidazolidinedione compounds topically *via* an appropriate ophthalmic solution applied dropwise to the eye.

The activity of the compounds of the present invention, as agents for the control of chronic diabetic complications, is determined by their ability to successfully pass one or more of the following standard biological or pharmacological tests, viz., (1) measuring their ability to inhibit the enzyme activity of isolated aldose reductase; (2) measuring their ability to reduce or inhibit sorbitol accumulation in the sciatic nerve of acutely streptozotocinized (i.e., diabetic) rats; (3) measuring their ability to reverse already-elevated sorbitol levels in the sciatic nerve and lens of chronic streptozotocin-induced diabetic rats; (4) measuring their ability to prevent or inhibit galactitol formation in the lens of acutely galactosemic rats, and (5) measuring their ability to delay cataract formation and reduce the severity of lens opacities in chronic galactosemic rats.

Preparation A

A solution consisting of 3.0 g. (0.014 mole) of ethyl ureidomalonate dissolved in 43 ml. of absolute ethanol was heated under reflux in a nitrogen atmosphere, while a 0.017 molar solution of sodium ethanolate (sodium in ethanol) was slowly added thereto over a period of 2.5 hours. Upon completion of this step, the resulting reaction mixture was cooled to room temperature (~20°C.) and the desired product collected by means of suction filtration and subsequently washed with two-20 ml. portions of absolute ethanol and one-20 ml. portion of absolute ether. In this manner, there was ultimately obtained pure sodio-ethyl hydantoin-5-carboxylate.

When the reaction was repeated using 10 g. of starting material (ethyl ureidomalonate) and 1.06 g of sodium in 60 ml. of absolute ethanol, the yield of pure final product amounted to 7.53 g. (85%).

Preparation B

A mixture consisting of 20 g. (0.14 mole) of 3-nitro-4-hydroxypyridine, 33.3 g. of phosphorous pentachloride and 2 ml. of phosphorus oxychloride was heated in an oil both at 130°C. for a period of three hours. Upon completion of this step, the excess phosphorus oxychloride was removed from the spent reaction mixture by means of fractional distillation and the residual material was subsequently taken up in methylene chloride. The latter solution was then washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent from the resulting filtrate then gave the desired product, viz., 3-nitro-4-chloropyridine.

When the procedure was repeated using 2.8 g. (0.02 mole) of starting material (3-nitro-4-hydroxy-pyridine), the yield of pure final product amounted to 2.35 g. (74%).

Preparation C

A solution consisting of 20.2 g. (0.182 mole) of *p*-fluoraniline and 22.1 g (0.182 mole) of *p*-fluorobenzaldehyde dissolved in 100 ml. of ethanol was refluxed for a period of five minutes. Upon completion of this step, the spent reaction mixture was cooled to room temperature (~20°C.) and the desired product subsequently collected by means of suction filtration. A second crop of product was thereafter obtained by concentrating the resulting filtrate *in vacuo*. The total yield of pure 3-[(*p*-fluorophenyl)methylidene)pyridine amounted to 33 g. (84%).

To 11.0 g. of the above intermediate in 50 ml. of methanol, there were added 1.92 g. of sodium borohydride at room temperature. Upon completion of this step, the resulting reaction mixture was diluted with water, extracted with diethyl ether and the ethereal extracts subsequently dried over anhydrous magnesium sulfate and filtered. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was ultimately obtained a crude residual product which thereafter crystallized from n-hexane to afford pure 3-[(*p*-fluorophenyl-aminomethyl]pyridine. The yield of pure product amounted to 8.6 g. (77%).

Example 1

A solution consisting of 500 mg. (0.230 mole) of *spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione [H. Otamasu et al., *Chem. Pharm. Bull.* (Tokyo), Vol. 23, No. 7, p. 1431 (1975)] dissolved in 10 ml. of dioxane

and 2 ml. of water was treated with chlorine gas by bubbling the gas through the mixture at room temperature (~20°C.) until saturation of same was complete with respect to said gas (this required a period of approximately two minutes). The course of the reaction was followed by means of thin layer chromatography (using acetone/hexane as the eluant) in order to ensure that no dichlorination occurred. Upon completion of this step, the reaction mixture was diluted with sodium sulfite solution and extracted with ethyl acetate to ultimately afford pure 5'-chloro-spiro-[imidazolidine-4,3'-indoline]-2,2',5-trione. The yield of pure product amounted to 150 mg. (26%).

A well-stirred mixture consisting of 300 mg. of 5'-chloro-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione, 48 ml. of glacial acetic acid and 16 ml of fuming nitric acid was heated at 90°C. for a period of one-half hour. Upon completion of this step, the cooled reaction mixture was poured into water, partially neutralized with sodium bicarbonate solution and the resulting product subsequently collected by means of suction filtration. In this manner, there was ultimately obtained 2.05 mg. (58%) of pure 5'-chloro-7'-nitro-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione, m.p. >270°C.

A solution consisting of 80 mg. of 5'-chloro-7'-nitro-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione dissolved in 5 ml. of ethanol containing 0.5 ml. of concentrated hydrochloric acid was treated with 10 mg. of 10% palladium on carbon catalyst and stirred in a hydrogen atmosphere at room temperature for a period of one hour. The resulting reaction mixture was then filtered thru filter-cel to remove the catalyst, which was thereafter washed with ethanol, and the combined washings and filtrate were subsequently concentrated *in vacuo* to afford a crude residual product. Recrystallization of the latter material from chloroform then gave pure 5'-chloro-7'-nitro-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione as the hydrochloride salt. The yield of pure material amounted to 56 mg. (68%). The pure product was characterized by means of high resolution mass spectroscopy (m/e, 266.0125; theory, 266.0177) and nuclear magnetic resonance data.

Example 2

A mixture of 1.0 g of a 50% dispersion of sodium hydride in mineral oil that had been covered with 50 ml. of dimethylformamide was treated with 2.16 g. of 5,7-dichloroindoline-2,3-dione (5,7-dichloroisatin) by adding the latter material slowly thereto in small portions. This was then followed by the addition of 1.64 g. of 3-pyridylmethylchloride and the resulting reaction mixture was heated at 90°C. for a period of one hour. Upon completion of this step, the spent reaction mixture was diluted with water, acidified and then extracted with ethylene acetate, followed by basification of the organic layer with aqueous sodium bicarbonate solution. The latter aqueous solution was then extracted with ethyl acetate, and the resulting organic layer saved and subsequently concentrated *in vacuo* to afford a crude residual product. Recrystallization of the latter material from diethyl/ether/ethyl acetate then gave 1.7 g. (55%) of pure 1-(3-pyridylmethyl) 5,7-dichloroindoline-2,3-dione.

A mixture consisting of 1.53 g of 1-(3-pyridylmethyl) 5,7-dichloroindoline-2,3-dione, 390 mg. of potassium cyanide and 1.86 g. of powdered ammonium carbonate in 40 ml. of 50% aqueous methanol was heated in an oil bath at 80°C. for a period of one-half hour. At the end of this time, the spent reaction mixture was cooled in an ice bath, quenched (i.e., acidified) with concentrated hydrochloric acid and diluted with additional water. After extracting the resulting aqueous solution with ethyl acetate, there were obtained several organic extracts that were later combined and subsequently dried over anhydrous magnesium sulfate to give a clear solution. Upon removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was ultimately obtained a residual material that was later chromatographed over 30 g. of silica gel using ethyl acetate as the eluant. The appropriate fractions were then combined and subsequently concentrated *in vacuo* to afford a pure solid residual material. Recrystallization of the latter material from ethanol/hexane then gave 750 mg. of pure 1'-(3-pyridymethyl)-5',7')dichloro-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione, m.p. 274°C. (decomp.). The pure product was further characterized by means of mass spectroscopy and nuclear magnetic resonance data.

Example 3

To a stirred solution consisting of 1.1 ml. of oxalyl chloride in 40 ml. of methylene chloride at 0°C., there was added in a dropwise fashion a clear solution consisting of 3-[(*p*-fluorophenyl)aminomethyl]pyridine (the product of Preparation C) dissolved in 30 ml. of methylene chloride. After stirring at room temperature (~20°C.) for five minutes, 2.7 g. of anhydrous aluminum chloride was added to the mixture in one full portion with the aid of vigorous agitation. The resulting reaction mixture was then refluxed for a period of 15 minutes. At the end of this time, the spent mixture was poured into ice water in order to decompose the aluminum chloride, neutralized with sodium bicarbonate and extracted with ethyl acetate. After drying the organic extract over anhydrous magnesium sulfate, the solvent was removed *in vacuo* and the residue crystallized from ethyl acetate to afford 1.25 g. (50%) of pure 1-(3-pyridylmethyl)-5-fluoroindoline-2,3-dione.

A mixture consisting of 1.024 g. of 1-(3-pyridylmethyl)-5-fluoroindoline-2,3-dione, 390 mg. of potassium cyanide and 1.86 g. of powdered ammonium carbonate in 40 ml. of 50% aqueous methanol was heated in an oil bath at 80°C. for a period of 20 minutes. At the end of this time, the spent reaction mixture was cooled in an ice bath, acidified with glacial acetic acid and diluted with additional water. After extracting the resulting aqueous solution with ethyl acetate, there were obtained several organic extracts

that were later combined and subsequently dried over anhydrous magnesium sulfate to give a clear solution. Upon removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was ultimately obtained a residual material that was later crystallized from ethyl acetate to afford 700 mg. (43%) of pure 1'-(3-pyridylmethyl)-5'-fluoro-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione. Recrystallization from methanol in the presence of activated carbon then gave an analytically pure sample, m.p. 202°C. (decomp.). The pure product was further characterized by means of mass spectroscopy and nuclear magnetic resonance data.

Example 4

A solution consisting of 2.0256 g. (0.01 mole) of 2,4-dinitrochlorobenzene and 2.384 g. (0.014 mole) of sodio-ethyl hydantoin-5-carboxylate (the product of Preparation A) dissolved in 10 ml. of dimethylformamide was allowed to stand at room temperature (~20°C) for a period of *ca.* 0.5—1.0 hour. Upon completion of this step, the spent reaction mixture was diluted with 50 ml. of water and extracted with two-25 ml. portions of ethyl acetate. The separated organic extracts were then combined and subsequently dried over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was ultimately obtained pure ethyl 5-(2,4-dinitrophenyl)hydantoin-5-carboxylate as the desired product.

A solution consisting of 0.3142 g. (0.001 mole) the above intermediate dissolved in 50 ml. of 50% aqueous ethanol was then brought to a rapid reflux, followed by the addition of 0.3351 g. (0.006 mole) of iron powder and 1 drop of concentrated hydrochloric acid to the stirred mixture. The resulting reaction mixture was then stirred mechanically for a period of *ca.* 0.5—1.0 hour. Upon completion of this step, the spent reaction mixture was neutralized with saturated aqueous sodium bicarbonate solution and the solvents were thereafter evaporated from the neutralized solution. In this manner, there was ultimately obtained pure 6'-amino-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione (m.p. >275°C.).

When the reaction was repeated using 2.63 g. of pure ethyl 5-(2,4-dinitrophenyl)hydantoin-5-carboxylate as starting material and with the aid of mechanical stirring for a period of three hours, the yield of the desired final product amounted to 1.5 g. (77%). The pure product was further characterized by means of mass spectroscopy and nuclear magnetic resonance data.

Example 5

A solution consisting of 639.2 mg. (0.00403 mole) of 3-nitro-4-chloropyridine (the product of Preparation B) and 1.0288 g. (0.0053 mole) of sodio-ethyl hydantoin-5-carboxylate (the product of Preparation A) dissolved in 10 ml. of dimethylformamide was allowed to stand at room temperature (~20°C.) overnight for a period of approximately 16 hours with the aid of mechanical stirring. Upon completion of this step, the solvent was evaporated from the mixture and the crude residual material was thereafter dried under a high vacuum and eventually crystallized from methylene chloride to afford 525 mg. of pure ethyl 5-(3-nitro-4-pyridyl)-hydantoin-5-carboxylate, m.p. 203.5—204.5°C.

When the reaction was repeated using 2.35 g. of 3-nitro-4-chloropyridine as starting material and 3.74 g. of sodio-ethyl hydantoin-5-carboxylate as the alkylating agent, the yield of pure product obtained amounted to 3.83 g. (88.3%).

A mixture consisting of 158.5 mg. (0.00054 mole) of ethyl 5-(3-nitro-4-pyridyl)hydantoin-5-carboxylate, 335.1 mg. of iron powder and 5 ml. of glacial acetic acid was heated to 100°C. and then cooled to *ca.* 65°C. The reaction was complete in approximately 10—15 minutes. Uppon completion of this step, the spent reaction mixture was filtered thru filter-cel in order to remove the unwanted solids and the resulting filtrate was subsequently evaporated under reduced pressure to finally afford pure *spiro*-[imidazolidine-4,3'-(6-azaindoline)]-2,2',5-trione as the desired final product. The yield of pure material melting at 265°C. (decomp.) amounted to 80 mg. (68%). The pure product was further characterized by means of mass spectroscopy and nuclear magnetic resonance data.

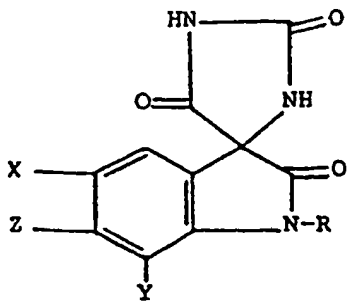
Example 6

The following *spiro*-oxindole imidazolidinedione final products of Examples 1—5, respectively, were tested at a concentration level of 10^{-6}M for their ability to reduce or inhibit aldose reductase enzyme activity *via* the procedure of S. Hayman et al., as described in the *Journal of Biological Chemistry*, Vol. 240, p. 877 (1965) and as modified by K. Sestanj et al. in U.S. Patent No. 3,821,383. In every case, the substrate employed was partially purified aldose reductase enzyme obtained from calf lens. The results obtained with each compound are expressed below in terms of their percent inhibition of enzyme activity (%) with respect to the particular concentration level chosen (10^{-6}M):

Compound	Inhibition at 10^{-6}M
Product of Example 1	72
Product of Example 2	82
Product of Example 3	71
Product of Example 4	27
Product of Example 5	49

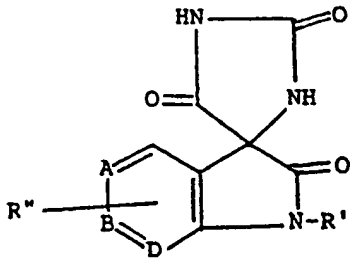
Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound selected from the group consisting of *spiro*-hydantoin derivatives of the formulae:



(I)

and



(II)

and the pharmaceutially acceptable salts thereof, wherein

X and Y are each hydrogen, fluorine, chlorine, bromine, nitro or amino;

Z is hydrogen or amino, with the proviso that Z is always other than amino when at least one of X and Y is other than hydrogen;

R is a member selected from the group consisting of hydrogen, aryl and aralkyl having up to three carbon atoms in the alkyl moiety wherein each of said aryl moieties is chosen from the group consisting of pyridyl and ring-substituted pyridyl, with each ring substituent being chosen from the group consisting of fluorine, chlorine, bromine and alkyl having from one to four carbon atoms, with the proviso that said R is always other than hydrogen when each of X, Y and Z is other than amino;

=A—B=D— of formula II represents =N—CH=CH—, =CH—CH=N— or =CH—N=CH—;

R' is a member selected from the group consisting of hydrogen, alkyl having from one to four carbon atoms, aryl and aralkyl having up to three carbon atoms in the alkyl moiety wherein each of said aryl moieties is chosen from the group consisting of pyridyl, thienyl, phenyl and mono and di-substituted phenyl, with each ring substituent being chosen from the group consisting of fluorine, chlorine, bromine, alkyl and alkoxy each having up to four carbon atoms with trifluoromethyl; and

R'' is hydrogen, hydroxy, fluorine, chlorine, alkyl or alkoxy each having up to four carbon atoms or trifluoromethyl.

2. A compound as claimed in claim 1 of the formula I wherein X is chlorine, Y is amino and Z is hydrogen and R is hydrogen.

3. A compound as claimed in claim 1 of the formula I wherein X and Y are each hydrogen, Z is amino and R is hydrogen.

4. A compound as claimed in claim 1 of the formula I wherein X is fluorine, Y and Z are each hydrogen and R is pyridylalkyl having up to three carbon atoms in the alkyl moiety.

5. A compound as claimed in claim 5 wherein R is 3-pyridylmethyl.

6. A compound as claimed in claim 1 of the formula I wherein X and Y are each chlorine, Z is hydrogen and R is pyridylalkyl having up to three carbon atoms in the alkyl moiety.

7. A compound as claimed in claim 6 wherein R is 3-pyridylmethyl.

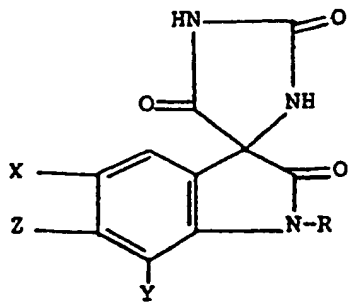
8. A compound as claimed in claim 1 of the formula II wherein =A—B=D— is =CH—N=CH—.

9. A compound as claimed in claim 8 wherein R' and R'' are each hydrogen.

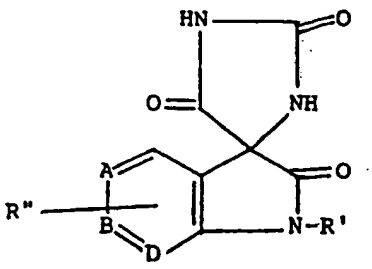
10. A pharmaceutical composition suitable for oral administration comprising a pharmaceutically acceptable carrier and a compound as claimed in claim 1 in an amount effective for the treatment of diabetes-associated chronic complications.

Claims for the Contracting State: AT

1. An analogy process for preparing *spiro*-hydantoin derivatives of the formulae:



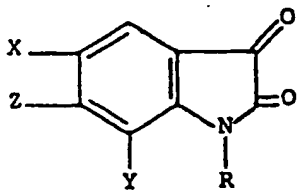
and



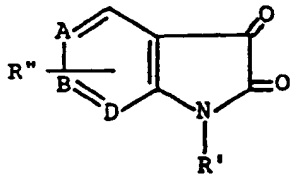
(I) (II)

and the pharmaceutially acceptable salts thereof, wherein X and Y are each hydrogen, fluorine, chlorine, bromine, nitro or amino; Z is hydrogen or amino, with the proviso that Z is always other than amino when at least one of X and Y is other than hydrogen; R is a member selected from the group consisting of hydrogen, aryl and aralkyl having up to three carbon atoms in the alkyl moiety wherein each of said aryl moieties is chosen from the group consisting of pyridyl and ring-substituted pyridyl, with each ring substituent being chosen from the group consisting of fluorine, chlorine, bromine and alkyl having from one to four carbon atoms, with the proviso that said R is always other than hydrogen when each of X, Y and Z is other than amino; =A—B=D— of formula II represents =N—CH=CH—, =CH—CH=N— or =CH—N=CH—; R' is a member selected from the group consisting of hydrogen, alkyl having from one to four carbon atoms, aryl and aralkyl having up to three carbon atoms in the alkyl moiety wherein each of said aryl moieties is chosen from the group consisting of pyridyl, thienyl, phenyl and mono and di-substituted phenyl, with each ring substituent being chosen from the group consisting of fluorine, chlorine, bromine, alkyl and alkoxy each having up to four carbon atoms with trifluoromethyl; and R'' is hydrogen, hydroxy, fluorine, chlorine, alkyl or alkoxy each having up to four carbon atoms or trifluoromethyl, characterized by:

(a) condensing an appropriately substituted carbonyl ring compound of the respectively formulae:



and



(III) (IV),

wherein X, Y, Z, R, R' and R'' are each as previously defined with an alkali metal cyanide and ammonium carbonate to form the corresponding *spiro*-oxindole imidazolidinedione final product of formula I or II;

(b) or when X and Y are each hydrogen and Z is amino in formula I, alkylating sodio-ethyl hydantoin-5-carboxylate with 2,4-dinitrobenzene, followed by reductive cyclization;

(c) or, when R' is hydrogen in formula II, alkylating sodio-ethyl hydantoin-5-carboxylate with an appropriate halonitro-disubstituted pyridine, followed by reductive cyclization;

(d) or, when X is halogen as previously defined, Y is amino and Z is hydrogen in formula I, halogenating the compound wherein X, Y and Z are each hydrogen to form the corresponding 5'-halo derivative wherein X is halogen, followed by nitration at the 7'-position and subsequent reduction;

and thereafter, if required, converting a compound of formula II wherein R' is hydrogen to a corresponding compound where R' is other than hydrogen;

and, if desired, converting a compound of formula I or II to a pharmaceutically acceptable salt thereof.

2. A process as claimed in part (a) of claim 1, characterized by the fact that at least a slight molar excess of the alkali metal cyanide reagent is employed with respect to the carbonyl ring compound starting material.

3. A process as claimed in part (a) of claim 1, characterized by the fact that said reaction is conducted in a reaction-inert polar organic solvent at a temperature that is in the range of from about 50°C. to about 150°C.

4. A process as claimed in claim 3, characterized by the fact that said solvent is a water-miscible lower alkanol.

5. The process as claimed in part (a) of claim 1, wherein the *spiro*-hydantoin derivative prepared is 1'-(3-pyridylmethyl)-5'-fluoro-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione.

6. The process as claimed in part (a) of claim 1, wherein the *spiro*-hydantoin derivative prepared is 1'-(3-pyridylmethyl)-5',7'-dichloro-*spiro*-[imidazolidine-4,3'-indoline)-2,2',5-trione.

7. A process as claimed in part (b) or (c) or claim 1, characterized by the fact that the reductive cyclization step is carried out with iron powder in the presence of an acid at a temperature that is in the range of from about 20°C. to about 100°C.

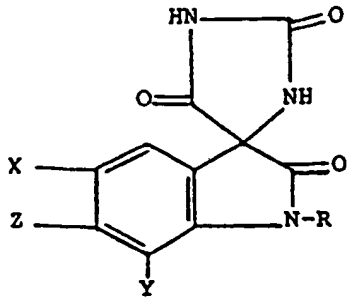
8. The process as claimed in part (c) of claim 1, wherein the *spiro*-hydantoin derivative prepared is *spiro*-[imidazolidine-4,3'-(6-azaindoline)]-2,2',5-trione.

9. A process as claimed in part (d) of claim 1, characterized by the fact that the reduction step is carried out by catalytic hydrogenation with a platinum, palladium or nickel catalyst.

10. The process as claimed in part (d) of claim 1, wherein the *spiro*-hydantoin derivative prepared is 5'-chloro-7'-amino-*spiro*-[imidazolidine-4,3'-(indoline)]-2,2',5-trione.

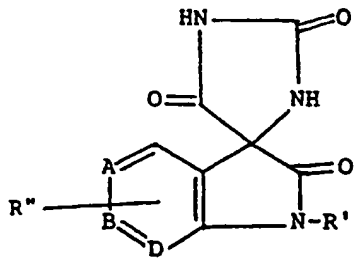
Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindung ausgewählt aus der Gruppe bestehend aus Spiro-Hydantoinderivaten der Formeln:



(I)

und



(II)

und die pharmazeutisch annehmbaren Salze hievon, worin

X und Y jeweils Wasserstoff, Fluor, Chlor, Brom, Nitro oder Amino sind;

Z Wasserstoff oder Amino ist, mit der Maßgabe, daß Z immer von Amino verschieden ist, wenn zumindest eines von X oder Y eine andere Bedeutung als Wasserstoff hat;

R ein Mitglied ausgewählt aus der Gruppe bestehend aus Wasserstoff, Aryl und Aralkyl mit bis zu drei Kohlenstoffatomen im Alkylteil ist, worin jeder der Arylteile aus der Gruppe bestehend aus Pyridyl und ringsubstituiertem Pyridyl ausgewählt ist, wobei jeder Ringsubstituent aus der Gruppe bestehend aus Fluor, Chlor, Brom und Alkyl mit ein bis vier Kohlenstoffatomen ausgewählt ist, mit der Maßgabe, daß R immer von Wasserstoff verschieden ist, wenn jedes von X, Y und Z eine andere Bedeutung als Amino hat;

=A—B=D— der Formel (II) =N—CH=CH—, =CH—CH=N— oder =CH—N=CH— bedeutet;

R' ein Mitglied ausgewählt aus der Gruppe bestehend aus Wasserstoff, Alkyl mit eine bis vier Kohlenstoffatomen, Aryl und Aralkyl mit bis zu drei Kohlenstoffatomen im Alkylteil ist, wobei jeder der Arylteile aus der Gruppe bestehend aus Pyridyl, Thienyl, Phenyl und mono- und disubstituiertem Phenyl ausgewählt ist, wobei jeder Ringsubstituent aus der Gruppe bestehend aus Fluor, Chlor, Brom, Alkyl und Alkoxy mit jeweils bis zu vier Kohlenstoffatomen und Trifluormethyl ausgewählt ist; und

R'' Wasserstoff, Hydroxy, Fluor, Chlor, Alkyl oder Alkoxy mit jeweils bis zu vier Kohlenstoffatomen oder Trifluormethyl ist.

2. Verbindung nach Anspruch 1 der Formel (I), worin X Chlor ist, Y Amino it und Z Wasserstoff ist und R Wasserstoff ist.

3. Verbindung nach Anspruch 1 der Formel (I), worin X und Y jeweils Wasserstoff sind, Z Amino ist und R Wasserstoff ist.

4. Verbindung nach Anspruch 1 der Formel (I), worin X Fluor ist, Y und Z jeweils Wasserstoff sind und R Pyridylalkyl mit bis zu drei Kohlenstoffatomen im Alkylteil ist.

5. Verbindung nach Anspruch 1 der Formel (I), worin R 3-Pyridylmethyl ist.

6. Verbindung nach Anspruch 1 der Formel (I), worin X und Y jeweils Chlor sind, Z Wasserstoff ist und R Pyridyllalkyl mit bis zu drei Kohlenstoffatomen im Alkylteil ist.

7. Verbindung nach Anspruch 6, worin R 3-Pyridylmethyl ist.

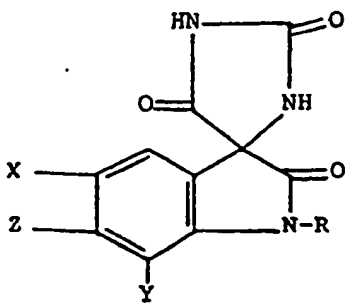
8. Verbindung nach Anspruch 1 der Formel (II), worin =A—B=D— die Bedeutung =CH—N=CH— hat.

9. Verbindung nach Anspruch 8, woring R' und R'' jeweils Wasserstoff sind.

10. Pharmazeutische Zusammensetzung geeignet zur oralen Verabreichung, umfassend einen pharmazeutisch annehmbaren Träger und eine Verbindung nach Anspruch 1 in einer Menge, die zur Behandlung von mit Diabetes assoziierten chronischen Komplikationen wirksam ist.

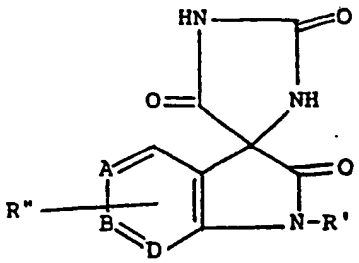
Patentansprüche für den Vertragsstaat: AT

1. Analogieverfahren zur Herstellung von Spiro-Hydantoinderivaten der Formeln:



(I)

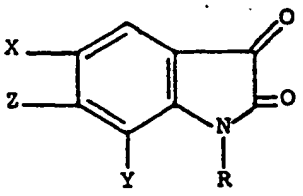
und



(II)

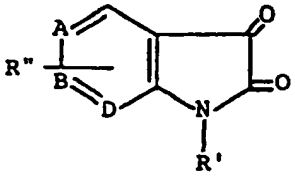
und der pharmazeutisch annehmbaren Salze hievon, worin X und Y jeweils Wasserstoff, Fluor, Chlor, Brom, Nitro oder Amino sind; Z Wasserstoff oder Amino ist, mit der Maßgabe, daß Z immer von Amino verschieden ist, wenn zumindest eines von X oder Y eine andere Bedeutung als Wasserstoff hat; R ein Mitglied ausgewählt aus der Gruppe bestehend aus Wasserstoff, Aryl und Aralkyl mit bis zu drei Kohlenstoffatomen im Alkylteil ist, worin jeder der Arylteile aus der Gruppe bestehend aus Pyridyl und ringsubstituiertem Pyridyl ausgewählt ist, wobei jeder Ringsubstituent aus der Gruppe bestehend aus Fluor, Chlor, Brom und Alkyl mit ein bis vier Kohlenstoffatomen ausgewählt ist, mit der Maßgabe, daß R immer von Wasserstoff verschieden ist, wenn jedes von X, Y und Z eine andere Bedeutung als Amino hat; =A—B=D— der Formel (II) =N—CH=CH—, =CH—CH=N— oder =CH—N=CH— bedeutet; R' ein Mitglied ausgewählt aus der Gruppe bestehend aus Wasserstoff, Alkyl mit ein bis vier Kohlenstoffatomen, Aryl und Aralkyl mit bis zu drei Kohlenstoffatomen im Alkylteil ist, wobei jeder der Arylteile aus der Gruppe bestehend aus Pyridyl, Thienyl, Phenyl und mono- und disubstituiertem Phenyl ausgewählt ist, wobei jeder Ringsubstituent aus der Gruppe bestehend aus Fluor, Chlor, Brom, Alkyl und Alkoxy mit jeweils bis zu vier Kohlenstoffatomen und Trifluormethyl ausgewählt ist; und R'' Wasserstoff, Hydroxy, Fluor, Chlor, Alkyl oder Alkoxy mit jeweils bis zu vier Kohlenstoffatomen oder Trifluormethyl ist, gekennzeichnet durch:

(a) das Kondensieren einer geeignet substituierten Carbonylringverbindung der Formeln:



(III)

und



(IV),

worin X, Y, Z, R, R' und R'' jeweils wie oben definiert sind, mit einem Alkalimetallcyanid und Ammoniumcarbonat unter Bildung des entsprechenden Spiro-Oxindolimidazolidindion-Endproduktes der Formel (I) oder (II);

(b) oder, wenn in Formel (I) X und Y jeweils Wasserstoff sind und Z Amino ist, das Alkylieren von Natriumäthylhydantoin-5-carboxylat mit 2,4-Dinitrobenzol gefolgt von reduzierender Cyclisierung;

(c) oder, wenn R' in Formel (II) Wasserstoff ist, das Alkylieren von Natriumäthylhydantoin-5-carboxylat mit einem geeigneten nitrohalogendisubstituierten Pyridin, gefolgt von reduzierender Cyclisierung;

(d) oder, wenn in Formel (I) X Halogen, wie oben definiert, ist, Y Amino ist und Z Wasserstoff ist, das Halogenieren der Verbindung, worin X, Y und Z jeweils Wasserstoff sind, unter Bildung des ent-

sprechenden 5'-Halogenderivatives, worin X Halogen ist, gefolgt von Nitrierung in der 7'-Stellung und anschließender Reduktion;

und danach, wenn erforderlich, daß Überführen einer Verbindung der Formel (II), worin R' Wasserstoff ist, in eine entsprechende Verbindung, worin R' eine andere Bedeutung als Wasserstoff hat;

und danach, gewünschtenfalls, das Überführen einer Verbindung der Formel (I) oder (II) in ein pharmazeutisch annehmbares Salz hievon.

2. Verfahren nach Teil (a) von Anspruch 1, dadurch gekennzeichnet daß zumindest ein leichter Molüberschuß des Alkalimetallcyanidreagens mit Bezug auf die Carbonylringverbindung als Ausgangsstoff verwendet wird.

3. Verfahren nach Teil (a) von Anspruch 1, dadurch gekennzeichnet, daß die Reaktion in einem reaktionsinerten polaren organischen Lösungsmittel bei einer Temperatur im Bereich von etwa 50 bis 150°C durchgeführt wird.

4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß das Lösungsmittel ein mit Wasser mischbares niedriges Alkanol ist.

5. Verfahren nach Teil (a) von Anspruch 1, worin das hergestellte Spiro-Hydantoinderivat 1'-(3-Pyridylmethyl)-5'-fluor-spiro-[imidazolidin-4,3'-indolin]-2,2',5-trion ist.

6. Verfahren nach Teil (a) von Anspruch 1, worin das hergestellte Spiro-Hydantoinderivat 1'-(3-Pyridylmethyl)-5',7'-dichlor-spiro-[imidazolidin-4,3'-indolin]-2,2',5-trion ist.

7. Verfahren nach Teil (b) oder (c) von Anspruch 1, dadurch gekennzeichnet, daß der reduzierende Cyclisierungsschritt mit Eisenpulver in Gegenwart einer Säure bei einer Temperatur im Bereich von etwa bis etwa 100°C durchgeführt wird.

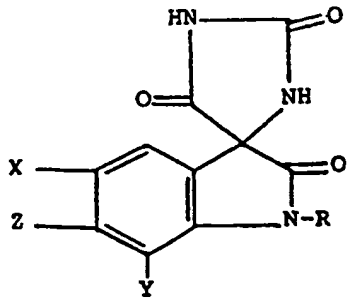
8. Verfahren nach Teil (c) von Anspruch 1, worin das hergestellte Spiro-Hydantoinderivat Spiro-[imidazolidin-4,3'-(6-azaindolin]-2,2',5-trion ist.

9. Verfahren nach Teil (d) von Anspruch 1, dadurch gekennzeichnet, daß der Reduktionsschritt durch katalytische Hydrierung mit eine Platin-, Palladium- oder Nickelkatalysator durchgeführt wird.

10. Verfahren nach Teil (d) von Anspruch 1, worin das hergestellte Spiro-Hydantoinderivat 5'-Chlor-7'-amino-spiro-[imidazolidin-4,3'-indolin]-2,2',5-trion ist.

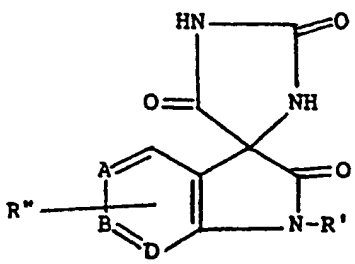
Revendications pour les Etats contractants: BE CH DE FR GB IT LI LY NL SE

1. Composé choisi dans le groupe comprenant des dérivés de *spiro*-hydantoïne aux formules:



(I)

et



(II)

et leurs sels pharmaceutiquement acceptables, formules dans lesquelles

X et Y représentent chacun l'hydrogène, le fluor, le chlore, le brome, un groupe nitro ou amino;

Z représente l'hydrogène ou un groupe amino, sous réserve que Z soit toujours un groupe différent d'un groupe amino lorsqu'au moins l'un des groupes X et Y est autre que l'hydrogène;

R est choisi entre l'hydrogène trois atomes de carbone dans le groupement alkyle, chacun desdits groupements aryle étant choisi entre des groupes pyridyle et pyridyle substitué sur le noyau, chaque substituant porté par le noyau étant choisi entre le fluor, le chlore, le brome et un groupe alkyle ayant un à quatre atomes de carbone, sous réserve que ledit groupe R soit toujours autre que l'hydrogène lorsque chacun des groupes X, Y et Z représente un groupe différent d'un groupe amino;

le groupe =A—B=D— dans la formule II représente un groupe =N—CH=CH—, =CH—CH=N— ou =CH—N=CH—;

R' est choisi entre l'hydrogène, des groupes alkyle ayant un à quatre atomes de carbone, aryle et aralkyle ayant jusqu'à trois atomes de carbone dans le groupement alkyle, chacun desdits groupements aryle étant choisi entre des groupes pyridyle, thiényle, phényle et phényle mono- et disubstitués, chaque substituant sur le noyau étant choisi entre le fluor, le chlore, le brome, des groupes alkyle et alkoxy ayant chacun jusqu'à quatre atomes de carbone, et trifluorométhyle; et

R'' représente l'hydrogène, un groupe hydroxy, le fluor, le chlore, un groupe alkyle ou alkoxy ayant chacun jusqu'à quatre atomes de carbone, ou trifluorométhyle.

2. Composé suivant la revendication 1, répondant à la formule I dans laquelle X représente le chlore, Y représente un groupe amino, Z représente l'hydrogène et R représente l'hydrogène.

3. Composé suivant la revendication 1, répondant à la formule I dans laquelle X et Y représentent chacun l'hydrogène, Z représente un groupe amino et R représente l'hydrogène.

4. Composé suivant la revendication 1, répondant à la formule I dans laquelle X représente le fluor, Y et Z représentent chacun l'hydrogène et R représente un groupe pyridylalkyle ayant jusqu'à trois atomes de carbone dans le groupement alkyle.

5. Composé suivant la revendication 4, dans lequel R représente un groupe 3-pyridylméthyle.

6. Composé suivant la revendication 1, répondant à la formule I dans laquelle X et Y représentent chacun le chlore, Z représente l'hydrogène et R représente un groupe pyridylalkyle ayant jusqu'à trois atomes de carbone dans le groupement alkyle.

7. Composé suivant la revendication 1, dans lequel R représente un groupe 3-pyridylméthyle.

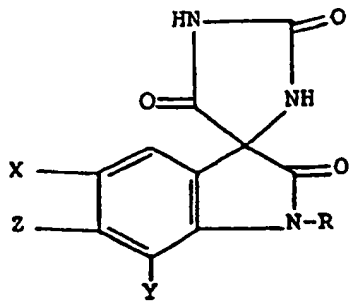
8. Composé suivant la revendication 1, répondant à la formule II dans laquelle le groupe =A—B=D— représente un groupe =CH—N=CH—.

9. Composé suivant la revendication 8, dans lequel R' et R'' représentent chacun l'hydrogène.

10. Composition pharmaceutique convenant pour l'administration orale, comprenant un support pharmaceutiquement acceptable et un composé suivant la revendication 1, en une quantité efficace pour le traitement des complications chroniques associées au diabète.

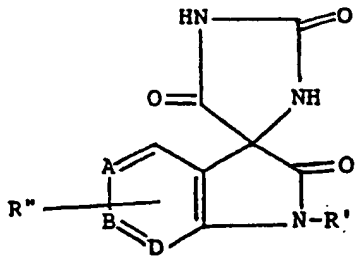
Revendications pour l'Etat contractant: AT

1. Procédé par analogie pour la préparation de dérivés de *spiro*-hydantoïne répondant aux formules:



(I)

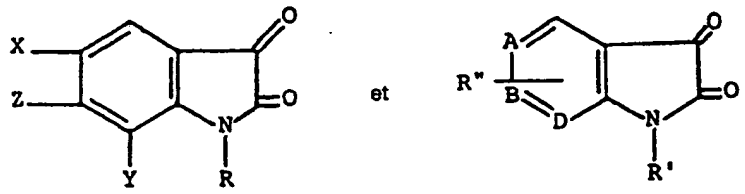
et



(II)

et de leurs sels pharmaceutiquement acceptables, formules dans lesquelles X et Y représentent chacun l'hydrogène, le fluor, le chlore, le brome, un groupe nitro ou amino; Z représente l'hydrogène ou un groupe amino, sous réserve que Z soit toujours un groupe différent d'un groupe amino lorsqu'au moins l'un des groupes X et Y est autre que l'hydrogène; R est choisi entre l'hydrogène trois atomes de carbone dans le groupement alkyle, chacun desdits groupements aryle étant choisi entre des groupes pyridyle et pyridyle substitué sur le noyau, chaque substituant porté par le noyau étant choisi entre le fluor, le chlore, le brome et un groupe alkyle ayant un à quatre atomes de carbone, sous réserve que ledit groupe R soit toujours autre que l'hydrogène lorsque chacun des groupes X, Y et Z représente un groupe différent d'un groupe amino; le groupe =A—B=D— dans la formule II représente un groupe =N—CH=CH—, =CH—CH=N— ou =CH—N=CH—; R' est choisi entre l'hydrogène, des groupes alkyle ayant un à quatre atomes de carbone, aryle et aralkyle ayant jusqu'à trois atomes de carbone dans le groupement alkyle, chacun desdits groupements aryle étant choisi entre des groupes pyridyle, thiényle, phényle et phényle mono- et disubstitués, chaque substituant sur le noyau étant choisi entre le fluor, le chlore, le brome, des groupes alkyle et alkoxy ayant chacun jusqu'à quatre atomes de carbone, et trifluorométhyle; et R'' représente l'hydrogène, un groupe hydroxy, le fluor, le chlore, un groupe alkyle ou alkoxy ayant chacun jusqu'à quatre atomes de carbone, ou trifluorométhyle, caractérisé en ce qu'il consiste:

(a) à condenser un composé à noyau carbonylé substitué de manière appropriée, répondant à l'une des formules:



(III) et (IV),

dans lesquelles X, Y, Z, R, R' et R'' répondent aux définitions précitées, avec un cyanure de métal alcalin et du carbonate d'ammonium pour former la *spiro*-oxindole-imidazolidinedione correspondante comme produit final de formule I ou II;

(b) ou, lorsque X et Y représésentent chacun l'hydrogène et Z représente un groupe amino dans la formule I, à alkyler le dérivé sodé d'hydantoïne-5-carboxylate d'éthyle avec le 2,4-dinitrobenzène, puis à effectuer une cyclisation réductrice;

(c) ou, lorsque R' représente l'hydrogène dans la formule II, à alkyler le dérivé sodé d'hydantoïne-5-carboxylate d'éthyle avec une pyridine à disubstitution halogéno-nitro appropriée, puis à effectuer une cyclisation réductrice;

(d) ou bien, lorsque X représente un halogène répondant à la dénition précitée, Y représente un groupe amino et Z représente l'hydrogène dans la formule I, à halogéner le composé dans lequel X, Y et Z représentent chacun l'hydrogène pour former le dérivé halogéné en 5' correspondant dans lequel X représente un halogène, puis à effectuer une nitration en position 7' et, ensuite, une réduction;

puis, si nécessaire, à transformer un composé de formule II, dans laquelle R' représente l'hydrogène, en un composé correspondant dans lequel R' est autre que l'hydrogène;

et, le cas échéant, à transformer un composé de formule I ou II en un de ses sels pharmaceutiquement acceptables.

2. Procédé suivant la partie (a) de la revendication 1, caractérise en ce qu'au moins un léger excés molaire du cyanure de métal alcalin servant de réactif est utilisé en ce qui concerne le composé à noyau carbonylé servant de matière de départ.

3. Procédé suivant la partie (a) de la revendication 1, caractérise en ce que la réaction est conduite dans un solvant organique polaire, inerte vis-à-vis de la reaction, à une température qui est comprise dans l'intervalle d'environ 50°C à environ 150°C.

4. Procédé suivant la revendication 1, caractérise en ce que le solvant est un alcanol inférieur miscible à l'eau.

5. Procédé suivant la partie (a) de la revendication 1, dans lequel le dérivé de *spiro*-hydantoïne préparé est la 1'-(3-pyridylméthyl)-5'-fluoro-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione.

6. Procédé suivant la partie (a) de la revendication 1, dans lequel le dérivé de *spiro*-hydantoïne préparé est la 1'-(3-pyridylméthyl)-5',7'-dichloro-*spiro*-[imidazolidine-4,3'-indoline]-2,2',5-trione.

7. Procédé suivant la partie (b) ou (c) de la revendication 1, caractérisé en ce que l'étape de cyclisation réductrice est effectuée avec la poudre de fer en présence d'un acide à une température qui est comprise dans l'intervalle d'environ 20°C à environ 100°C.

8. Procédé suivant la partie (c) de la revendication 1, dans lequel le dérivé de *spiro*-hydantoïne préparé est la *spiro*-[imidazolidine-4,3'-(6-azaindoline)]-2,2',5-trione.

9. Procédé suivant la partie (d) de la revendication 1, caractérisé en ce que l'étape de réduction est effectuée par hydrogénation catalytique avec un catalyseur au platine, au palladium ou au nickel.

10. Procédé suivant la partie (d) de la revendication 1, dans lequel le dérivé de *spiro*-hydantoïne préparé est la 5'-chloro-7'-amino-*spiro*-[imidazolidine-4,3'-(indoline)]-2,2',5-trione.